

CHAPTER 162

Nephrotic Syndrome and Proteinuria

ETIOLOGY AND EPIDEMIOLOGY

Small amounts of protein are found in urine of healthy children ($<4\text{ mg/m}^2/\text{hour}$ or urine protein/creatinine [U_{Pr}/Cr] $<0.2\text{ mg/mg}$). **Nephrotic proteinuria** in children is defined as protein excretion greater than $40\text{ mg/m}^2/\text{hour}$ or U_{Pr}/Cr greater than 2 mg/mg . Proteinuria between these levels is mildly to moderately elevated but not nephrotic. There are three general patterns of proteinuria: transient, orthostatic (postural), and persistent (fixed). Nephrotic syndrome is a subset of massive persistent proteinuria.

Transient proteinuria can be seen in children with fever, dehydration, or following seizure or vigorous exercise; it resolves within a few days, does not indicate renal disease, and needs no further evaluation or treatment.

Orthostatic (postural) proteinuria is a benign condition defined by normal protein excretion while recumbent but mild proteinuria (U_{Pr}/Cr $0.2\text{--}1\text{ mg/mg}$) when upright. Orthostatic proteinuria is more common in adolescents and tall, thin individuals; it is not associated with progressive kidney disease. Many children with orthostatic proteinuria continue this process into adulthood.

Persistent (fixed) proteinuria indicates intrinsic kidney disease. Most persistent proteinuria is **glomerular** in origin and characterized by a combination of large and small molecular weight proteins, variable levels of proteinuria, and, often, other evidence of glomerular disease (hematuria, red blood cell casts, hypertension, and renal insufficiency). **Tubular** proteinuria is characterized by preponderance of low molecular weight proteins and is seen in conditions of tubulointerstitial injury. Patients with tubular proteinuria may have a negative urine dipstick since this test specifically measures urinary albumin. The combination of tubular proteinuria with tubular electrolyte wasting and glycosuria is termed **Fanconi syndrome**.

Nephrotic syndrome (NS) is defined as persistent heavy proteinuria (mainly albuminuria; $>40\text{ mg/m}^2/\text{hour}$), **hypoalbuminemia** (serum albumin $<3.0\text{ g/dL}$), **hypercholesterolemia** ($>250\text{ mg/dL}$), and **edema**. Urinary protein losses occur due to abnormalities in the glomerular epithelial cell or podocyte and/or basement membrane that usually restricts protein filtration. The resultant massive proteinuria leads to decreased serum albumin and reduction in plasma oncotic pressure, leading to fluid shifts from vascular to interstitial compartments and plasma volume contraction. Edema results from decreased oncotic pressure as well as increase in tubular sodium reabsorption from reduced effective circulating blood

TABLE 162.1 Primary and Secondary Forms of Nephrotic Syndrome (NS)

PRIMARY NS

Minimal change NS
Primary focal segmental glomerulosclerosis
Idiopathic membranous nephropathy
Hereditary NS (congenital NS, infantile NS)

SECONDARY NS

Systemic lupus erythematosus and other glomerulonephritides (e.g., MPGN, PIGN)
IgA vasculitis, granulomatosis with polyangiitis and other vasculitides
Chronic infections (hepatitis B, hepatitis C, malaria, HIV)
Allergic interstitial nephritis
Diabetes
Amyloidosis
Malignancies

IgA, Immunoglobulin A; MPGN, membranoproliferative glomerulonephritis; PIGN, postinfectious glomerulonephritis.

volume. Hypoalbuminemia stimulates hepatic lipoprotein synthesis and diminishes lipoprotein metabolism, leading to elevated serum lipids (cholesterol, triglycerides) and lipoproteins.

There are three main causes of NS in children and a number of less common secondary causes (Table 162.1). **Minimal change nephrotic syndrome (MCNS)** is the most common histologic form of primary NS in children. More than 80% of children less than 7 years of age with NS have MCNS. Children 7–16 years old with NS have a ~50% chance of having MCNS. Males are affected more frequently than females (2:1), and the peak age of presentation is in the preschool years.

Focal segmental glomerulosclerosis (FSGS) accounts for ~10–20% of children with NS. Children with FSGS may present like those with MCNS or with less severe proteinuria. Some experts believe there is a spectrum of disease from MCNS to FSGS. A circulating factor that increases glomerular permeability is found in some patients with FSGS. More than 35% of children with FSGS progress to end-stage kidney disease.

Membranous nephropathy represents less than 5% of children with NS. It is seen most commonly in adolescents and children with systemic infections (hepatitis B, syphilis, malaria, and toxoplasmosis), exposure to specific medications (gold, penicillamine), or with autoimmune disease such as systemic lupus erythematosus.

NS may be a feature of more severe cases of any type of glomerulonephritis including immunoglobulin A (IgA) nephropathy, IgA vasculitis (Henoch-Schönlein purpura nephritis), postinfectious glomerulonephritis, and membranoproliferative glomerulonephritis. NS may also occur due to several secondary causes including amyloidosis, nonsteroidal antiinflammatory drug exposure, and lymphoma (see Table 162.1).

Congenital NS (CNS) presents during the first 3 months of life. The most common cause is Finnish type CNS, a rare autosomal recessive disorder that is caused by a mutation in nephrin, a component of the podocyte slit diaphragm. A heterogeneous group of other disorders, including diffuse mesangial sclerosis and conditions associated with drugs or congenital infections, may also cause CNS. **Infantile NS** presents between 3 and 12 months of age and is usually caused by mutations in genes encoding other proteins of the glomerular filtration barrier.

CLINICAL MANIFESTATIONS

Children with NS initially present with facial and periorbital edema that progresses to more widespread edema including abdominal swelling, lower extremity edema, and even anasarca. The early stages of disease may be mistaken for an allergic reaction. Initial presentation often follows an immune trigger such as an upper respiratory infection. Anorexia, malaise, abdominal pain, diarrhea (due to intestinal wall edema), and respiratory distress (due to presence of ascites and/or pleural effusion) may be present. MCNS is characterized by *absence* of gross hematuria, renal dysfunction, and hypertension.

DIAGNOSTIC STUDIES

Proteinuria of 1+ or higher on two to three first-morning urine specimens suggests persistent proteinuria that should be further evaluated. A U_{Pr}/Cr less than 0.2 mg/mg on a first-morning specimen suggests orthostatic proteinuria, and no further evaluation is needed. U_{Pr}/Cr greater than 0.2 mg/mg indicates abnormal proteinuria, with values greater than 2 mg/mg indicative of nephrotic range proteinuria.

Children with persistent proteinuria should have kidney function assessed with serum creatinine, electrolyte panel, and albumin level. Routine testing typically includes a serum C3 complement. In children with NS, a low serum C3 implies a lesion other than MCNS. Renal ultrasound is often useful to rule out structural abnormalities of the urinary tract. Renal biopsy is recommended in children with persistent proteinuria including NS when MCNS is not suspected (e.g., kidney dysfunction, age >13 years, presence of hematuria, and hypertension).

TREATMENT

Because greater than 80% of children less than 13 years of age with NS have steroid-responsive forms (chiefly MCNS), empiric steroid therapy may be initiated without a renal biopsy if a child has typical features of MCNS. Typical initial therapy for MCNS is prednisone, 2 mg/kg per day (60 mg/m² per day, maximum 60 mg/day), provided once a day or split into two doses for 6 weeks followed by 1.5 mg/kg (40 mg/m², maximum 40 mg/day) once every other day for an additional 6 weeks. Over 90% of children who respond to steroids do so within 4 weeks. A renal biopsy is indicated for nonresponders as steroid resistance decreases the chance that MCNS is the underlying disease. Relapses of NS are treated with shorter courses of high-dose steroids. Children with frequent relapses or steroid resistance may require additional immunosuppressive therapy.

Treatment responses in FSGS are highly variable. Approximately 35% of children respond to steroid therapy; others may respond to additional immunosuppressive therapy. Membranous nephropathy often improves with immunosuppressive therapy but does not reliably remit with standard NS steroid therapy. Infants with congenital or infantile NS do not respond to immunosuppression and are treated with supportive care, aggressive nutritional support, dialysis, and transplantation.

The cornerstone to edema management is dietary salt restriction. Severe edema may require use of loop diuretics or fluid restriction. When these therapies are not successful,

cautious parenteral administration of 25% albumin (0.5–1 g/kg intravenously over 2–4 hours) followed by an intravenous loop diuretic may achieve diuresis. Supportive strategies include elevation of the legs or other body parts with severe swelling, careful monitoring of daily weights, and if inpatient, tracking of intake and output.

COMPLICATIONS

Side effects of steroids, such as increased appetite and irritability, are most common in steroid-dependent and frequently relapsing patients who have greatest exposure to steroids. Hypovolemia and even acute kidney injury may result from diarrhea or overaggressive diuresis. Serious infections, including **bacteremia** and **peritonitis** (particularly *Streptococcus pneumoniae*, *Escherichia coli*, or *Klebsiella*), may occur due to urinary loss of immunoglobulins and complement. **Throm-boembolism** (TE) including deep vein thrombosis, central sinus thrombosis, renal vein thrombosis, and pulmonary embolism may occur due to a hypercoagulable state caused by urinary losses of coagulation factors, antithrombin, and plasminogen. Although routine anticoagulation is not recommended in children with NS, it may be considered in those with a history of prior TE or at particularly high risk. Persistent hyperlipidemia in children with steroid-resistant NS promotes increased risk of atherosclerotic vascular disease.

PROGNOSIS

Nearly 80% of children with steroid-responsive MCNS experience at least one NS relapse, defined as heavy proteinuria that persists for 3 or more consecutive days. Relapse patterns include **infrequently relapsing**, **frequently relapsing** (four or more relapses/year), and **steroid-dependent** (relapse within 2 weeks of steroid discontinuation). Some children do not respond to steroids initially, or despite initial response they become **steroid resistant**. Steroid-responsive patients have little risk of progressive chronic kidney disease. Patients who are steroid resistant, however, are more likely to progress to end-stage kidney disease (see [Chapter 165](#)). Recurrence of disease occurs in ~30% of children with steroid-resistant FSGS who undergo renal transplantation.

PEARLS FOR PRACTITIONERS

See *Nephrology and Urology: Pearls for Practitioners* at the end of this section.

CHAPTER 163

Glomerulonephritis and
Hematuria

ETIOLOGY AND EPIDEMIOLOGY

Hematuria, defined as five or more red blood cells (RBCs) per high-power field on freshly voided and centrifuged urine, is a common clinical issue in pediatrics. Hematuria may originate

TABLE 163.1 Differential Diagnosis of Red Urine/Hematuria

FACTITIOUS HEMATURIA
Nonpathologic (urate crystals in infants, ingested foods, medications, dyes) Pathologic (hemoglobinuria from hemolytic anemia, myoglobinuria from rhabdomyolysis)
GLOMERULAR
Immunologic injury (GN—e.g., PIGN, IgA nephropathy, MPGN, systemic diseases) Structural disorder (Alport syndrome, thin basement membrane disease) Toxin-mediated injury (HUS)
TUBULOINTERSTITIAL/PARENCHYMAL
Inflammation (interstitial nephritis, pyelonephritis) Vascular (sickle cell trait/disease, nutcracker syndrome) Structural (cyst rupture, Wilms tumor, urinary tract obstruction, renal trauma)
LOWER URINARY TRACT
Inflammation (cystitis, hemorrhagic cystitis, urethritis) Injury (trauma, kidney stone) Hypercalciuria

GN, Glomerulonephritis; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; MPGN, membranoproliferative glomerulonephritis; PIGN, postinfectious glomerulonephritis.

from glomerular, tubulointerstitial, or lower urinary tract disorders (Table 163.1). **Microscopic hematuria** is found in up to 5% of healthy children but in most cases is a transient finding and resolves on repeated testing. Persistent microscopic hematuria may indicate a number of conditions including glomerular disease, crystalluria, or inherited disorders such as sickle cell trait/disease or polycystic kidney disease. **Macroscopic (gross) hematuria** indicates visible blood in the urine and may be seen in conditions such as urolithiasis, urinary tract infection, and **acute glomerulonephritis (GN)**. **Postinfectious glomerulonephritis (PIGN)** is the most common form of acute GN and immunoglobulin A (IgA) nephropathy is the most common form of chronic GN; however, many other types of GN can occur.

CLINICAL MANIFESTATIONS

Children with acute GN commonly present with hematuria (macro- or microscopic) and other cardinal features of glomerular injury (proteinuria, hypertension, edema, oliguria, acute kidney injury). PIGN occurs most frequently in children 2–12 years of age and is more common in boys. Manifestations of PIGN are typical of acute GN and follow infections with bacterial and viral pathogens. PIGN most commonly develops on average 10 days after streptococcal pharyngitis and 4–6 weeks after impetigo. Antibiotic treatment of streptococcal or other infections does not prevent or delay development of GN.

IgA nephropathy has a more variable presentation and may take the form of acute GN, asymptomatic microscopic hematuria, or the classic presentation of recurrent macroscopic hematuria concurrent with an upper respiratory infection. Children with GN secondary to IgA vasculitis (Henoch-Schönlein

purpura), systemic lupus erythematosus, and vasculitis typically present with other systemic features of the respective condition.

Rapidly progressive glomerulonephritis (RPGN) is a more severe form of acute GN with a rapid loss of kidney function over days to weeks. RPGN may be seen in any form of acute GN. A common feature on renal biopsy is glomerular epithelial cell proliferation with crescents. Early recognition and treatment of RPGN is crucial to prevent progression to end-stage kidney disease (ESKD).

Alport syndrome is caused by mutations in genes encoding type IV collagen, which lead to construction of abnormal glomerular basement membrane (GBM) in the kidneys and ears. The most common inheritance pattern is X linked, but autosomal dominant and recessive forms exist. Males with Alport syndrome present with either painless microscopic or macroscopic hematuria, progressive proteinuria, hypertension, loss of kidney function, and sensorineural hearing loss. Females typically have a more benign course with microscopic hematuria but in some cases may develop ESKD. **Thin basement membrane disease** (benign familial hematuria) is caused by autosomal dominant collagen mutations that lead to isolated GBM thinning and persistent hematuria. There is often a family history of benign hematuria in first-degree relatives. As opposed to Alport syndrome, thin basement membrane disease is typically not progressive and usually has an excellent prognosis.

Nonglomerular causes of hematuria have a more variable presentation related to the underlying etiology. **Urinary tract infection (UTI)** is typically associated with dysuria and urinary frequency. **Urolithiasis** may be associated with flank or abdominal pain, although some children with stones are asymptomatic. **Hypercalciuria** can cause either macroscopic or microscopic hematuria with classic symptoms of UTI but without pyuria or a positive urine culture. **Strenuous exercise, sickle cell trait/disease, or Wilms tumor** may cause painless macroscopic hematuria. **Autosomal dominant polycystic kidney disease** or **nutcracker syndrome** (renal vein compression) may be associated with macroscopic hematuria with flank pain. Hematuria following **trauma** may signify more severe renal or lower urinary tract injury.

DIAGNOSTIC STUDIES

All patients with hematuria should have a careful history and physical (including blood pressure) along with urinalysis including microscopic examination to identify RBCs. Glomerular hematuria is suggested by brownish (tea- or cola-colored) urine and presence of RBC casts and/or dysmorphic RBCs on urine microscopy. A urine color that is more bright red without RBC casts or dysmorphic RBCs is more suggestive of a lower urinary tract source.

Children with macroscopic and microscopic hematuria with associated concerning findings should have additional evaluation. A suggested algorithm for the evaluation of hematuria is given in Fig. 163.1. In patients with suspected GN, complement C3 should be measured as hypocomplementemia narrows the differential diagnosis to PIGN, membranoproliferative GN, and lupus nephritis. Renal ultrasound is helpful in ruling out tumor, hydronephrosis, and urolithiasis. Urine calcium and creatinine ($U_{Ca/Cr}$) ratio may screen for hypercalciuria; abnormal findings (>0.2 mg/mg) should be confirmed with a 24-hour urine collection for calcium and creatinine.

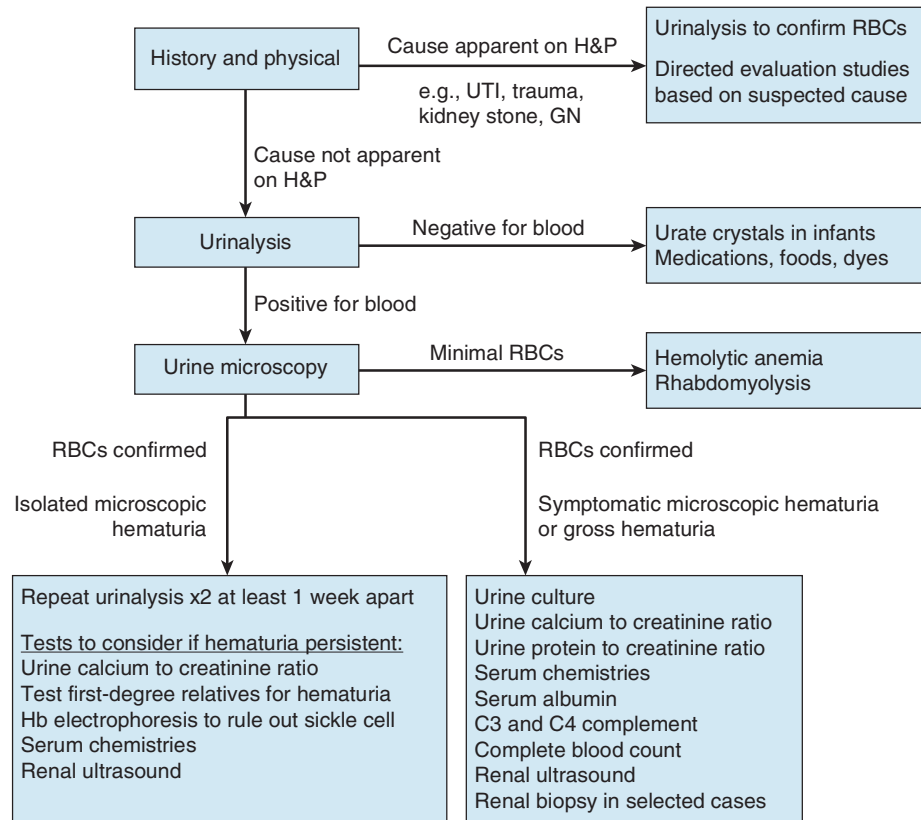


FIGURE 163.1 Suggested algorithm for evaluation of red urine/hematuria. GN, Glomerulonephritis; Hb, hemoglobin; H&P, history and physical; RBCs, red blood cells; UTI, urinary tract infection.

Children with isolated, asymptomatic microscopic hematuria with negative evaluation may be observed with yearly urinalyses. If hematuria is persistent, or the child develops proteinuria, hypertension, or loss of kidney function, nephrology referral for additional evaluation is appropriate.

TREATMENT

Treatment of PIGN involves supportive care with dietary sodium restriction, diuretics, and antihypertensive agents. Although treating the streptococcal infection does not prevent PIGN, antibiotic treatment is warranted with active streptococcal infection. Treatment of children with other forms of GN depends on underlying cause and severity and may include corticosteroids and/or other immunosuppressive agents. Treatment with angiotensin-converting enzyme inhibitors may reduce proteinuria and glomerular hyperperfusion but should be used with caution in the setting of acute kidney injury.

PROGNOSIS AND PREVENTION

PIGN usually has a favorable outcome. In typical cases, the gross hematuria, proteinuria, and edema decline quickly (5–10 days), while microscopic hematuria may persist for months or even years; greater than 95% of children recover completely with no long-term sequelae.

Children with IgA nephropathy and other forms of chronic GN have greater risk of progression to ESKD, which is variable and related to the underlying disorder and disease severity. The

presence of persistent and heavy proteinuria, hypertension, decreased kidney function, and severe glomerular lesions on renal biopsy are associated with poor outcomes.

Children with idiopathic isolated, asymptomatic microscopic hematuria or suspected thin basement membrane disease typically have an excellent renal prognosis. Long-term follow-up, including yearly urinalysis and blood pressure measurement, is required to exclude progressive forms of kidney disease.

PEARLS FOR PRACTITIONERS

See *Nephrology and Urology: Pearls for Practitioners* at the end of this section.

CHAPTER 164

Hemolytic Uremic Syndrome

ETIOLOGY AND EPIDEMIOLOGY

Hemolytic uremic syndrome (HUS) is characterized by the triad of **microangiopathic hemolytic anemia**, **thrombocytopenia**, and **acute kidney injury (AKI)**. The most common form of HUS is associated with **Shiga-toxin producing *Escherichia coli* (STEC)** and is termed **STEC-HUS**. Children with STEC-HUS experience a prodromal diarrheal illness due to hemorrhagic enterocolitis following exposure to a

pathogenic agent (most commonly *E. coli* O157:H7). STEC-HUS outbreaks have been associated with contaminated ground beef, fruit, vegetables, or water. STEC-HUS occurs in ~5–15% of children with STEC infection.

HUS may also occur unrelated to STEC infection (**non-STEC-HUS**). Infection with *Streptococcus pneumoniae* or HIV has been associated with non-STEC-HUS. Genetic and acquired defects in complement regulation, medications, malignancy, systemic lupus erythematosus, and pregnancy may also be associated with non-STEC-HUS. The clinical course of non-STEC-HUS is usually more severe than STEC-HUS and more likely to lead to chronic kidney disease.

Less commonly, children may develop a similar microangiopathic syndrome, identified as **thrombotic thrombocytopenic purpura** (TTP). Children with TTP typically have predominantly central nervous system (CNS) symptoms but may also have significant kidney disease. Because CNS involvement is also seen in HUS, TTP can be difficult to distinguish from HUS. Children with TTP have severe deficiency of ADAMTS13, a von Willebrand factor–cleaving protease.

CLINICAL MANIFESTATIONS

STEC-HUS typically occurs in children less than 5 years of age but can occur in older children. Classic STEC-HUS begins with enterocolitis, often with bloody stools, followed in 7–10 days by weakness, lethargy, and oliguria/anuria. Physical examination reveals irritability, pallor, and petechiae. Volume depletion is common at presentation; however, some children have volume overload. Hypertension may be present due to volume overload and/or renal injury. CNS involvement, including seizures, occurs in up to 25% of cases. Other potential organ involvement includes pancreatitis, cardiac dysfunction, and colonic perforation. Children with non-STEC-HUS have similar clinical presentation but usually without a recent history of enterocolitis.

DIAGNOSTIC STUDIES

Common laboratory findings in HUS are listed in Table 164.1. Peripheral blood smear reveals evidence of microangiopathic hemolysis with schistocytes and thrombocytopenia. Coombs test is negative. Serum blood urea nitrogen and creatinine are elevated consistent with AKI, and associated electrolyte abnormalities may be present. Serologic and stool studies may confirm presence of Shiga toxin, although the toxin may no longer be present by the time of diagnosis of HUS. ADAMTS13 level is normal in all forms of HUS but is deficient in TTP.

TREATMENT AND PROGNOSIS

Therapy for STEC-HUS is supportive and includes volume repletion, treatment of hypertension, and managing complications of AKI, including dialysis when indicated. Early and aggressive intravenous hydration with isotonic saline during the diarrheal phase may lessen the severity of AKI. Red blood cell transfusions are provided as needed. Platelet transfusions should be reserved for active hemorrhage or prior to invasive procedures as they may fuel the thrombotic microangiopathy process. Antibiotics and anti-diarrheal agents should be avoided in children with STEC

TABLE 164.1 Common Laboratory Findings with Hemolytic Uremic Syndrome

EVIDENCE OF MICROANGIOPATHIC HEMOLYTIC ANEMIA

Anemia
Thrombocytopenia
Presence of schistocytes, helmet cells, and burr cells on peripheral blood smear
Increased LDH
Decreased haptoglobin
Increased indirect bilirubin
Increased AST
Elevated reticulocyte count

EVIDENCE OF RENAL INJURY

Elevated serum creatinine
Oliguria
Presence of hematuria, proteinuria, pyuria, casts on urinalysis

OTHER POTENTIAL FINDINGS

Leukocytosis
Positive stool culture for *E. coli* O157:H7
Positive stool test for Shiga toxin
Elevated amylase/lipase

AST, Aspartate aminotransferase; *E. coli*, *Escherichia coli*; LDH, lactate dehydrogenase.

infection as they increase the risk of developing HUS. Most children (>95%) with STEC-HUS survive the acute phase and recover normal kidney function, although some may have evidence of chronic kidney disease and other morbidity. Treatment of non-STEC-HUS depends on the underlying etiology.

PEARLS FOR PRACTITIONERS

See *Nephrology and Urology: Pearls for Practitioners* at the end of this section.

CHAPTER 165

Acute Kidney Injury and Chronic Kidney Disease

ACUTE KIDNEY INJURY

Etiology

Acute kidney injury (AKI), formerly termed *acute renal failure*, refers to an abrupt decrease in glomerular filtration rate (GFR) leading to accumulation of waste products (e.g., urea) and disturbance in fluid and electrolyte homeostasis. AKI may be **oliguric** (<1 mL/kg/hr in neonates and infants, <0.5 mL/kg/hr in children) or **nonoliguric**, which may be more difficult to recognize.

Causes of AKI may be divided into prerenal (renal hypoperfusion), intrinsic renal (tubular, glomerular, or vascular injury), and postrenal (urinary tract obstruction) categories (Table 165.1). In many cases, the cause of AKI is multifactorial. **Prerenal AKI** is most commonly due to **volume depletion** but may be secondary to other mechanisms of glomerular

hypoperfusion. **Intrinsic AKI** may be due to **acute tubular necrosis** (ATN), which can be caused by a hypoxic-ischemic insult and/or exposure to nephrotoxic agents (medications, contrast, myoglobin). Acute glomerulonephritis, acute tubulointerstitial nephritis, and vascular thromboses are other causes of intrinsic renal AKI. **Postrenal AKI** occurs due to conditions that result in either structural or functional **urinary tract obstruction**.

TABLE 165.1 Causes of Acute Kidney Injury

PRERENAL
Dehydration
Hemorrhage
Septic shock
Burns
Heart failure
Cirrhosis
POSTRENAL (OBSTRUCTION)
Urethral obstruction (stricture, posterior urethral valves)
Ureteral obstruction
Ureterocele
Extrinsic tumor compressing bladder outlet
Neurogenic bladder (myelomeningocele, spinal cord injury)
INTRINSIC
Acute tubular necrosis
Nephrotoxins (medications, contrast, myoglobin)
Infection (sepsis)
Interstitial nephritis
Glomerular injury (primary glomerulonephritis, vasculitis, hemolytic uremic syndrome)
Vascular (renal vein thrombosis, arterial emboli, malignant hypertension)

Clinical Manifestations

History, physical examination, and basic studies usually allow proper classification of the child with AKI (Table 165.2). Prerenal AKI is characterized by history of precipitating factors leading to volume depletion. Urine output is low. Intrinsic AKI from ATN is associated with precipitating factors such as prolonged hypotension or exposure to nephrotoxic agents. Urine output in ATN may be low, normal, or high, depending on the severity of the injury. Children with glomerulonephritis present with hematuria, edema, hypertension, and oliguria. In postrenal AKI, urine output may be low or normal and may be associated with flank masses or a distended bladder on examination. Depending on the underlying cause and severity of illness, AKI can be associated with signs of dehydration or volume overload.

Diagnostic Studies

Early recognition and management of AKI is crucial. A **urinalysis** (UA) should be obtained in all children with AKI. In children with prerenal AKI, the UA is unremarkable with high specific gravity reflecting appropriate urinary concentration. Neonates, children with preexisting kidney disease, and individuals with sickle cell disease may not be able to concentrate urine well despite volume depletion. In children with AKI from glomerular and vascular injury, hematuria and proteinuria are usually moderate to severe. In children with oliguric AKI, differentiation between prerenal AKI and ATN may be made by determining urine osmolality and fractional excretion of sodium (see Table 165.2). **Renal ultrasound** is helpful in evaluation of obstructive or postrenal AKI (see Table 165.2). Renal biopsy is indicated only in select cases of intrinsic AKI.

Common electrolyte abnormalities seen in AKI include hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia. These labs should be trended over time, the frequency of which depends on initial results and the patient's clinical course. A complete blood count should be measured as anemia is frequently observed in children with AKI. Other laboratory studies may be obtained as clinically indicated.

TABLE 165.2 Laboratory and Clinical Evaluation of Acute Kidney Injury

LABORATORY/CLINICAL FEATURE	PRERENAL		RENAL		POSTRENAL
	CHILD	NEONATE	CHILD	NEONATE	
Urine output	Low		Low, normal, or high		Low or normal
Urinalysis	Normal		RBCs, WBCs, protein, casts		Variable
Urine Na ⁺ (mEq/L)	<15	<20–30	>40	>50	Variable, may be >40
FE _{Na} [*] (%)	<1	<2.5	>2	>2.5	Variable, may be >2
Urine osmolality (mOsm/L)	>500	>350	~300	~300	Variable, may be <300
Renal ultrasound	Normal		Increased echogenicity, decreased corticomedullary differentiation		Hydronephrosis

*FE_{Na} (%) = [(urine sodium/plasma sodium) ÷ (urine creatinine/plasma creatinine)] × 100.
FE_{Na}, Fractional excretion of sodium; RBCs, red blood cells; WBCs, white blood cells.

Treatment

In some cases, treating the underlying disorder will improve AKI. Examples include volume repletion in dehydration, stopping an offending nephrotoxic medication, and relieving urinary tract obstruction. In all cases, efforts should be made to limit additional kidney injury (e.g., ensuring adequate renal perfusion and avoiding nephrotoxic medications). Medication dosages and intervals should be adjusted for decreased GFR as appropriate.

Initial approach to fluid therapy depends on the child's volume status and urine output. If hypovolemia is present, intravascular volume should be expanded using intravenous saline administration. If hypervolemia is present, 1–2 mg/kg of furosemide and fluid restriction is indicated. If euvolemia is present, total fluid input should be adjusted to match insensible losses and urine output, which may be higher or lower than normal. All children with AKI should have careful measurement of intake and output as well as serial body weight measurements and physical examination with attention to volume status.

Treatment of AKI involves prevention and management of potential complications, including electrolyte abnormalities. Potassium intake and medications that increase potassium should be restricted. If hyperkalemia occurs, intravenous calcium will lower the risk of arrhythmia while measures are initiated to shift potassium into cells (bicarbonate, β -agonists, insulin/dextrose) and hasten removal (diuretics, sodium-potassium exchange resins, dialysis). Hyperphosphatemia should be treated with phosphorus restriction and administration of phosphate binders. Hypertension may be treated with diuretics, calcium channel blockers, and vasodilators. Angiotensin-converting enzyme (ACE) inhibitors are usually avoided in the setting of AKI.

Indications for **acute dialysis** (kidney support therapy) are listed in Table 165.3. There is no specific blood urea nitrogen or creatinine level at which dialysis is needed in patients with AKI. Renal replacement options in children include peritoneal dialysis, hemodialysis, and continuous renal replacement therapy. The mode is selected based on individual factors.

Prognosis

Recovery from AKI depends on the etiology and severity of AKI and other patient characteristics. Preterm infants who experience AKI prior to completion of renal development are

at particularly high risk. Even with seemingly good recovery, a history of moderate to severe AKI, especially if dialysis support was required, places the child at increased risk for future chronic kidney disease (CKD).

CHRONIC KIDNEY DISEASE

Etiology and Epidemiology

Congenital anomalies of the kidney and urinary tract (CAKUT), such as renal dysplasia, are the most common causes of CKD in children. Acquired kidney diseases, such as focal segmental glomerulosclerosis and glomerulonephritis (GN), are more common causes of CKD in older children and teens. The risk of progression to end-stage kidney disease (ESKD) is related to the underlying cause and severity of CKD. Kidney function may deteriorate more rapidly during puberty due to increased demands of growth and maturation.

CKD is staged to facilitate appropriate evaluation and monitoring according to estimated GFR (Table 165.4). GFR can be estimated in children using the Schwartz formula (see Chapter 161). Most metabolic complications of CKD do not begin to manifest until at least stage 3 CKD. In stage 4 CKD, complications become more numerous and severe. Children with stage 5 CKD (ESKD) require treatment with either dialysis or kidney transplantation.

Clinical Manifestations

The clinical presentation of a child with CKD is related to both the underlying etiology and stage of CKD at time of diagnosis. A child with CAKUT may have polyuria, polydipsia, and recurrent urinary tract infections. A child with GN may have hematuria, proteinuria, edema, and hypertension. Common complications of CKD in children are listed in Table 165.5. Most of these complications are multifactorial in etiology. For example, **anemia** results primarily from a failure to produce adequate **erythropoietin** as well as iron deficiency. **Growth failure** may result from poor nutrition, metabolic acidosis, hormonal abnormalities, resistance to growth hormone, and **CKD-mineral bone disorder (CKD-MBD)**. CKD-MBD is usually due to **secondary hyperparathyroidism** as a result of hyperphosphatemia, hypocalcemia, and diminished renal 1,25-dihydroxyvitamin D production. If prolonged and/or severe, CKD-MBD may lead

TABLE 165.3 Indications for Renal Replacement Therapy

ACUTE AND/OR CHRONIC DIALYSIS
Volume overload
Metabolic acidosis
Electrolyte abnormalities
Uremia
ACUTE DIALYSIS
Certain ingestions
Hyperammonemia
CHRONIC DIALYSIS
Poor growth
Stage 5 chronic kidney disease (end-stage kidney disease)

TABLE 165.4 Classification of the Stages of Chronic Kidney Disease

STAGE	GFR (ML/MIN/1.73 M ²)*	DESCRIPTION
1	>90	Minimal kidney damage
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15 (or dialysis)	End-stage kidney disease

*GFR ranges apply for children age ≥ 2 yr.

From National Kidney Foundation Kidney Disease Outcomes Quality Initiative. GFR, Glomerular filtration rate.

to rickets and bone deformities. **Hypertension** and **left ventricular hypertrophy** are common cardiovascular complications. Delayed puberty results from altered gonadotropin secretion and regulation. Learning and school performance may also be impaired in children with CKD.

Treatment

The management of children with advanced CKD requires a multidisciplinary team, which ideally includes a pediatric nephrologist, renal dietitian, social worker, and psychologist. Adequate nutrition should be ensured even if it requires dietary supplements and tube feedings. Some infants and young children with CAKUT require supplemental salt due to urinary sodium wasting. Conversely, children with GN require salt restriction to assist in management of hypertension or edema. Common treatment considerations for CKD complications are listed in Table 165.5.

Several measures can be taken to preserve kidney function or slow progression of CKD. ACE inhibitors or angiotensin receptor blockers should be used to reduce proteinuria and control blood pressure. Potentially nephrotoxic medications such as ibuprofen should be avoided when feasible. Medication adjustment for reduced kidney function is important. Protein intake is typically not restricted in pediatric CKD due to growth needs.

Children with stage 5 CKD (ESKD) require either kidney transplantation or dialysis support. The optimal treatment of ESKD is **kidney transplantation**. **Maintenance dialysis** is effective for a child awaiting kidney transplantation or when kidney transplantation is not possible. **Peritoneal dialysis** is done at home by the family. **Hemodialysis** is performed three

times a week at a dialysis facility. Indications for chronic dialysis are listed in Table 165.3.

Prognosis

Children with mild CKD (stages 1 and 2) are usually asymptomatic but need to be monitored for progressive loss of kidney function. Children with stages 3 and 4 CKD have a high likelihood of progressing to ESKD at some point, although the timing can vary. Because children on maintenance dialysis have the highest morbidity and mortality, the goal is to provide a kidney transplant for all children with ESKD. Children with kidney transplants generally do well but must take lifelong immunosuppressive medications associated with a variety of side effects, including infections, nephrotoxicity, cardiovascular complications, and increased risk for certain malignancies. Transplanted kidneys can last for more than 10–20 years, but eventually fail, requiring re-transplantation.

PEARLS FOR PRACTITIONERS

See *Nephrology and Urology: Pearls for Practitioners* at the end of this section.

TABLE 165.5 Common Complications and Treatments of Chronic Kidney Disease

COMPLICATION	TREATMENT
1. Poor growth	Increased caloric intake, treat acidosis, treat CKD-MBD, recombinant GH
2. Anemia	Erythropoietin, iron supplementation
3. CKD–Mineral bone disorder/secondary hyperparathyroidism	1,25-dihydroxyvitamin D supplementation, calcium supplementation, dietary phosphorous restriction, phosphate binders
4. Cardiovascular	
4a. Hypertension	Antihypertensive medications
4b. Left ventricular hypertrophy	Volume control
5. Electrolyte abnormalities	
5a. Hyperkalemia	Low K diet, furosemide, sodium polystyrene sulfonate
5b. Hyponatremia	Sodium supplementation
5c. Metabolic acidosis	Alkali replacement

CKD, Chronic kidney disease; CKD-MBD, chronic kidney disease—mineral bone disorder; GH, growth hormone; K, potassium.